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Hematopoietic Stem Cell Transplantation in Multiple Myeloma

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ABSTRACT

High-dose therapy and autologous hematopoietic stem cell transplantation are standard early treatment of patients with multiple myeloma. Tandem transplantation appears to provide additional benefit, particularly in patients with limited response to initial transplantation. Myeloablative allogeneic transplantation provides the only potential for cure, but has been largely abandoned because of high mortality rates. Newer and better induction regimens, rigorous analysis of results with autologous and allogeneic transplantation, and the development of risk-adapted stratification provide the impetus for this critical evaluation of the role of hematopoietic stem cell transplantation in multiple myeloma.

KEY WORDS

Multiple myeloma • Hematopoietic stem cell transplantation

INTRODUCTION

The median survival of patients with multiple myeloma is approximately 4 years. This malignancy is virtually incurable, and accounts for 20% of all deaths because of hematologic malignancies. Further, it is a progressively debilitating disease characterized by bone pain, spontaneous fractures, frequent infections, renal failure, and anemia. Because of its potential to dramatically affect quality of life, the time spent in remission is important. Despite controversy about the effectiveness and precise role of hematopoietic stem cell transplantation (HSCT) in multiple myeloma, this disorder is presently the most common for which HSCT is used. New transplant approaches including double transplants, safer regimens for allogeneic transplantation, and maintenance therapy may improve outcome. The integration of newer agents including thalidomide, lenalidomide, and bortezomib into conventional treatment promises to improve nontransplant approaches, causing some to question the need for transplantation. In this review, we summarize relevant background information and discuss the role of hematopoietic stem cell transplantation in multiple myeloma.

CURRENT OUTCOMES WITH AUTOLOGOUS TRANSPLANTATION

Single Autotransplantation

Large prospective randomized trials [1,2] and several nonrandomized comparisons [3-8] established for most clinicians that in patients aged 65 or less with no significant organ impairment, high-dose therapy and autologous transplantation following initial conventional therapy improve rates of response, complete remission (CR), overall survival (OS), and event-free survival (EFS) compared to continued conventional therapy. Also, the time without symptoms, treatment and treatment toxicity (TWIsTT) was longer for patients who underwent transplantation [9]. Results of autologous transplantation have improved largely through reduction of transplant-related morbidity and mortality (TRM) using modern supportive care, including the use of mobilized peripheral blood stem cells in place of marrow and preparation with melphalan rather than radiation-containing regimens [10]. The TRM rate following autotransplantation is now <2%. A recent evidence-based review recommended autotransplantation, using melphalan and peripheral

Table 1. *Major Randomized Prospective Trials with Single Autologous Stem Cell Transplantation in Multiple Myeloma*

Trial	Author	Year	No. of Patients	Median Age	Conditioning Regimen	Survival
Intergroupe Francophone du Myelome 90	Attal, et al. (2)	1996	200	57	Melphalan 140 and TBI	Superior progression free survival (18 versus 27 mo., $P = .01$) and overall survival (37.4 mo. versus not reached) with transplant versus conventional chemotherapy
Medical Research Council Myeloma VII	Child, et al. (1)	2003	401	55	Melphalan 200	Superior progression free survival (31.6 mo. versus 19.6 mo., $P < .001$) and overall survival (54 mo. versus 42 mo., $P = .04$) with transplant vs. conventional chemotherapy
HOVON*	Segeren et al. (13)	2003	261	55	Cyclophosphamide 120 mg/kg and TBI	No difference in progression free survival (22 mo. versus 21 mo., $P = .28$) and overall survival (47 mo. versus 50 mo., $P = .41$) with transplant versus conventional chemotherapy
PETHEMA†	Blade, et al. (14)	2005	216	56	Melphalan 200, Melphalan 140 and TBI	No difference in progression free survival (42 mo. versus 33 mo., $P = .57$) and overall survival (61 mo. versus 66 mo., $P = .89$) with transplant versus conventional chemotherapy
Myelome Autogreffe 91	Fermand et al. (9)	2005	190	61	Melphalan 200, melphalan 140 and busulphan	No difference in progression free survival (25.3 mo. versus 18.7 mo., $P = .07$) and overall survival (47.8 mo. versus 47.6 mo., $P = .91$) with transplant versus conventional chemotherapy
Intergroup S 9321	Barlogie et al. (12)	2006	516	54	Melphalan 140 and TBI	No difference in progression free survival (7 year estimate 17% and 16%.) and overall survival (7 year estimate 37% and 42 %mo.) with transplant vsersus conventional chemotherapy

TBI indicates total-body irridiation.
*HOVON: Dutch-Belgian Hemato-Oncology Cooperative Study Group.
†PETHEMA: Programa para el Tratamiento de Hemopatias Malignas.

blood stem cells, in preference to standard chemotherapy as de novo treatment [11].

Some randomized studies comparing autotransplantation to conventional therapy, however, have not demonstrated a significant survival benefit [9,12-14]. The differences in outcome between trials (Table 1) may be related to variations in eligibility criteria, induction therapy, preparative regimens, duration of follow-up, and the use of transplantation at relapse. For example, the conditioning regimens vary and those used in some studies are probably suboptimal(13). Benefit from transplantation may not be demonstrable for several years, but some studies do not provide lengthy follow-up [13,14]. The Spanish Programa para el Tratamiento de Hemopatias Malignas (PETHEMA) group randomized only those patients who achieved a response to induction chemotherapy [14]. Yet patients who fail to respond, benefit from autotransplantation [15]. Despite these limitations of the reports, it is important that a meta-analysis of randomized controlled trials demonstrated a significant benefit in progression-free survival (PFS), but not OS with a single early autotransplant [16]. It is reasonable to conclude that autotransplantation provides a significant benefit in PFS and TWIsTT. A significant survival benefit for early transplantation has not been clearly demonstrated, but the frequent use of later transplantation complicates interpretation of this finding.

Double Autotransplantation

Barlogie and colleagues [17,18] introduced the concept of tandem transplants, which have subsequently been investigated in several randomized trials [19-23]. Attal and colleagues [21] compared single to double autologous transplantation in patients under 60 years of age following 3 or 4 courses of chemotherapy. At 6 years, OS and EFS were doubled in the tandem transplant group. The survival benefit was magnified in those with less than a very good partial response (PR) following the first transplant. These results were supported by a randomized prospective study (Bologna 96) that demonstrated that tandem HSCT benefits patients who are not in at least a near CR after the first transplant [22]. Data from the Arkansas group shows a survival advantage in patients who underwent tandem transplantation compared to

historic controls who underwent a single procedure. A recent update of patients undergoing tandem transplantation at Arkansas demonstrated a 10-year EFS of 18% and OS of 23% [24].

Tandem transplants do require increased time in the hospital and may not benefit patients who achieve CR or very near CR after the first transplantation [21,22]. The quality of life at 1 year appears worse after tandem transplantation [20]. Last, patients with specific cytogenetic abnormalities may not benefit substantially from tandem transplantation [25,26].

Nevertheless, these studies established the benefit of double transplantation in most patients aged under 60 who have a limited response to a single transplant. The second transplant should be performed within 3 to 6 months after the first. Patients who do not complete 2 transplants within 12 months have a worse prognosis [24].

Maintenance Therapy following Autologous Transplantation

Interferon maintenance following autotransplantation initially seemed beneficial [27,28], but many patients experienced toxicity. Subsequent randomized trials incorporating interferon failed to demonstrate a significant survival benefit [12,29].

Thalidomide was used by the Arkansas group during induction, between the 2 transplants, and following transplantation until disease progression or significant adverse affects [30]. Thalidomide increased the rates of response and EFS, but not OS, because of a poorer outcome after relapse. Also, 30% of patients taking thalidomide experienced a thrombotic event and 27% experienced grade 3 or 4 peripheral neuropathy.

The Intergroupe Francophone du Myelome (IFM) 99-02 study, which did not use thalidomide earlier in treatment, demonstrated a benefit in EFS and OS in patients randomized to thalidomide and pamidronate after tandem transplant. Adverse events necessitated discontinuation of thalidomide in 39% of patients [31]. Thalidomide appeared to benefit patients with residual disease following transplantation, raising doubt about the appropriateness of the term "maintenance." Lower doses of thalidomide are being evaluated after tandem transplantation [32]. The present common use of thalidomide in induction may compromise its effectiveness in maintenance. Bortezomib is also under investigation as maintenance therapy [33].

Elderly Patients

Most studies of autotransplantation in myeloma have been carried out in the nonelderly, thus excluding a large proportion of myeloma patients [34]. The feasibility and efficacy of transplantation in patients over 70 years of age was demonstrated in a nonrandomized study by the Arkansas group, utilizing a lower dose of melphalan than is used in younger patients [35]. A multicenter prospective study demonstrated a higher response rate and significantly better EFS and OS in patients undergoing tandem transplants using intermediate dose melphalan [36].

In a trial of patients over 65 years of age, however, thalidomide in combination with melphalan and prednisone resulted in superior PFS and OS compared to transplantation following induction with melphalan and prednisone [37]. This study did not address whether autotransplantation following the more effective induction regimen would provide additional benefit. Thus, whereas transplantation can be safely performed and is effective in selected patients over the age of 65, its superiority to present nontransplant approaches is uncertain.

Timing of Transplantation

A prospective randomized study demonstrated similar survival in patients irrespective of whether transplantation was performed early or at the time of relapse [38]. The TWiSTT, however, was better in the group undergoing early transplantation. A nonrandomized study demonstrated that patients transplanted within 1 year of primary therapy fared better than those who underwent late transplant [39]. Based on these data, autotransplantation should generally be performed early in the course of disease.

Purging

$CD34^+$ selection reduced the tumor burden in the graft by more than 3 logs, but PFS and OS were not improved [40]. A study of genetically marked grafts demonstrated no contribution of infused myeloma cells to relapse [41], emphasizing that the main cause of relapse is the failure to eradicate myeloma in the patient.

Quality of Life

Myeloma is a debilitating disease with frequent relapses. It can devastate quality of life. The Nordic Myeloma Group demonstrated lower quality of life scores at 1 and 6 months in patients who underwent transplantation, but better scores in this group at 36 months [42]. The TWiSTT score was better in the transplantation group compared to that receiving only conventional chemotherapy in the Myelome-Autogreffe (MAG) trial [9]. Quality of life is also better when patients undergo transplant early compared to after relapse [38]. It is vital that parameters assessing the quality of life be included in the design of trials studying transplantation in multiple myeloma.

Cost versus Benefit of Autotransplant

Early studies comparing the cost effectiveness of transplant to conventional chemotherapy were retro-

spective and involved small numbers of patients [43,44]. Gulbrandsen and colleagues [45] prospectively compared melphalan-prednisone to autologous transplant. They used quality-adjusted life-years, a product of 2 factors: the change in quality of life that follows from an intervention and the number of years gained as a result of treatment. The cost of high-dose therapy and stem cell transplantation was justified by the considerable gain in patient's quality-adjusted life-years.

CURRENT OUTCOMES WITH ALLOGENEIC TRANSPLANTATION

Myeloablative Transplantation

In contrast to autologous transplantation, allogeneic transplantation can cure patients with myeloma [46]. This approach assures the absence of myeloma cells in the graft and provides the potential for a graft-versus-myeloma effect [47]. The targets of graft-versus-myeloma (and graft-versus-host disease [GVHD]) are minor histocompatibility antigens recognized by donor T cells. T cell responses to antigens restricted to hematopoietic cells can mediate an effective antitumor reaction without GVHD. More widely expressed minor histocompatibility antigens may be targets for GVHD and a graft-versus-myeloma effect. Following a donor lymphocyte infusion-induced sustained complete remission in a patient with multiple myeloma, van Bergen and colleagues [48] isolated a cytotoxic T lymphocyte-clone capable of recognizing the minor antigen encoded by the ATP-dependent interferon responsive gene, which was highly expressed on the myeloma cells. Expression of the relevant minor histocompatibility antigens on malignant stem cells, those rare cells with the ability to perpetuate themselves through self-renewal and to generate differentiated malignant plasma cells, are probably required for cure of malignancy by the allogeneic effect [49].

Allogeneic transplantation in patients with multiple myeloma has generally resulted in a high incidence of TRM [12,46,50-53]. Mortality following unrelated transplantation has been particularly frequent [53]. Allotransplantation does, however, significantly lower relapse rates [50], and a modest proportion of patients appear to be cured. Despite providing the only potential for cure, the substantial mortality rates, exceeding 40% in many studies, have been considered prohibitive by most clinicians.

Generally, the high mortality rates have been associated with transplantation of patients with advanced disease who had received multiple chemotherapy regimens. The Seattle group reported a mortality rate in excess of 50%, but noted that for patients who underwent transplantation within a year from diagnosis, mortality was <20% [50]. Early transplantation and careful selection of patients is crucial to achieve favorable outcomes using allogeneic transplantation in most hematologic malignancies [49]. These factors may be particularly critical in patients with myeloma who tolerate allotransplantation poorly, perhaps related to their underlying immunodeficiency and the debilitating nature of their disease. The recently published U.S. intergroup trial originally included an allogeneic transplant arm that was closed after 36 patients were treated, because of a mortality rate of 53% [12]. These allogeneic patients were treated, following completion of induction chemotherapy with high-dose cyclophosphamide to mirror the autologous transplantation arm of the trial. They subsequently received preparation for transplantation with melphalan plus total body irridiation (TBI). The high-dose cyclophosphamide coupled with the intensive preparative regimen may have contributed to the high mortality in this vulnerable population. Despite the early deaths, 7-year survival is identical for autologous and allogeneic recipients, and PFS is 22% for allogeneic recipients with a plateau extending up to 10 years. Substantially higher rates of sustained PFS following allogeneic transplantation have been reported [51,52].

The European Group for Blood and Marrow Transplantation compared results in patients with myeloma who underwent allogeneic transplantation from fully matched siblings from 1994 through 1998 to those who underwent transplantation prior to 1994 [54]. Survival was significantly improved in patients who underwent the procedure after 1994 because of a significant reduction in deaths from interstitial pneumonia and infections. Transplant-related mortality was reduced to 21% at 6 months and 30% at 2 years, with no difference between those receiving bone marrow or peripheral blood. The patients transplanted after 1994 benefited from less previous treatment and better supportive care.

Although numerous myeloablative preparative regimens have been used, their influence on outcome has been inadequately studied. Prospective comparisons have not been performed. The suspicion that TBI may not be well tolerated by patients with myeloma and older individuals has led to extensive use of radiation-free regimens, including bulsulfan and cyclophosphamide [50] and busulfan and melphalan [55].

The use of less toxic regimens is particularly critical in multiple myeloma. Dose adjustment [56] and/or intravenous administration of busulfan [57] appear to lower TRM rates and improve effectiveness in other disorders. A large study of targeted busulfan preceding autotransplantation in myeloma reported no venoocclusive disease [58].

Considering recent results with lower mortality rates, the absence of other curative treatments, and the debilitating nature of this disease, allotransplantation seems understudied and underutilized. As with auto-

transplantation, the potential benefit of allotransplantation must be balanced against its risk. Patients must be fully informed of both.

Reduced-Intensity Regimens

The significant risk of dying from complications of fully ablative transplantation stimulated exploration of reduced-intensity preparative regimens for allotransplantation. The Seattle group utilized a nonablative regimen of 200 cGy TBI and fludarabine with posttransplant immunosuppression with mycophenolate and cyclosporine in a small series of patients, many with advanced myeloma [59,60]. Safety was demonstrated, but no durable complete responses were obtained. Other groups have used various reduced-intensity regimens to achieve lower TRM, however, relapse rates are much higher than for standard preparative regimens and PFS appears similar or inferior to that with myeloablative transplants [60,61]. Patients with aggressive disease and plasmacytomas fare particularly poorly. As with ablative transplantation, poor functional status, advanced disease, and chemoresistant disease are adverse risk factors for TRM, PFS, and OS [62].

Sequential Autologous and Nonablative Allogeneic Transplantation

Temporal separation of the high-dose preparation and the immune effects of the allograft (Figure 1) may be a safer way to provide potentially curative therapy [63-66]. TRM of 10% to 20% has been reported, but late TRM and relapse require further study. A prospective trial by Bruno and colleagues [65] reported superior OS and EFS in those undergoing allograft following autograft compared to tandem autografts, whereas a similar study in high-risk individual failed to demonstrate such a difference [66].

CURRENT OUTCOMES WITH NONTRANSPLANT THERAPIES

Melphalan and prednisone (MP) produce responses in more than 50% of patients [67,68]. Subsequently developed regimens, including VBMCP (vincristine, carmustine, melphalan, cyclophosphamide, and prednisone), high-dose steroids, and VAD (vincristine-adriamycin-dexamethasone) produce similar response rates [69-72]. CRs occur rarely with these regimens.

New agents are improving treatment. Oral thalidomide-dexamethasone (thal-dex) resulted in significantly higher rates of response than treatment with dexamethasone alone [73] or intravenous VAD [74], although CR was achieved in <5% of patients. The addition of thalidomide to MP (MPT) improves response rate, CR rate, EFS, and OS [37,75].

The proteasome inhibitor bortezomib was more effective than high-dose dexamethasone in patients with advanced disease [76]. In a phase 1/2 trial, the combination of bortezomib, melphalan, prednisone, and thalidomide achieved CR in a striking 36% of a subgroup treated for first relapse [77]. These encouraging results, particularly the high rate of CR, provide a basis for study in early stage disease, where a randomized phase 3 trial is underway. At present, there is insufficient long-term follow-up on patients receiving newer regimens to determine their effect on the benefit provided by transplantation.

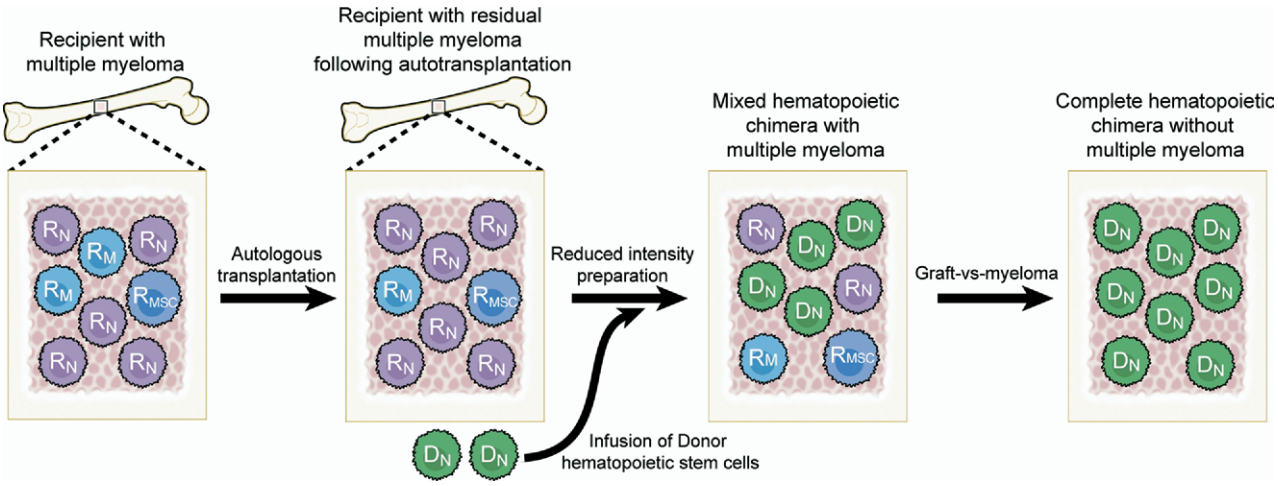

Figure 1. Theory of autologous followed by nonablative allogeneic transplantation. A recipient with multiple myeloma has normal (R_N) and multiple myeloma (R_M) and myeloma stem cells (R_{MSC}) in the marrow prior to autologous transplantation. Following high-dose therapy and autotransplantation, the number of malignant cells is reduced. Allogeneic hematopoietic stem cell transplantation following nonablative preparation permits engraftment of normal donor hematopoietic cells (D_N). Immunologic eradication of recipient normal and malignant cells results in complete donor hematopoietic chimerism.

RELEVANCE OF COMPLETE REMISSIONS

Although clinical response is desirable and is commonly considered an accurate predictor of survival, neither the rapidity nor degree of response reliably predicts survival [78,79]. Time to progression was a better predictor of survival than response to frontline therapy for more than 1500 patients enrolled on 4 Southwest Oncology Group myeloma studies [79]. A large study from M.D. Anderson did show significant survival benefit when a PR was converted to CR or no response to PR by autotransplantation [80].

The degree of response reflects the short-term effect of treatment on differentiated malignant plasma cells, which constitute nearly the entire malignancy. Cure, however, depends on elimination of the exceedingly rare self-renewing malignant stem cells from which the terminally differentiated malignant plasma cells are derived [81,82]. Myeloma stem cells are biologically distinct from their differentiated counterparts [83,84].

The malignant stem cells are quiescent and resistant to most chemotherapy, which acts predominantly on proliferating cells. Additionally, they excrete toxic drugs and resist apoptosis [85]. Chemotherapy may destroy nearly all of a patient's myeloma cells (achieving remission) without affecting malignant stem cells. Bortezomib and lenalidomide also inhibit differentiated malignant plasma cells but have little effect in vitro on myeloma stem cells [82,86]. These stem cells result in recurrence, the timing of which depends largely on the biologic aggressiveness of a particular patient's myeloma. Thus, CR may be a valid surrogate of survival in patients with biologically indolent disease, but not in those with aggressive disease.

CURRENT STATUS OF PROGNOSTIC FACTORS

Several laboratory parameters have prognostic value in multiple myeloma and different combinations of factors have been used to categorize patients and predict prognosis. Most poor-risk factors, including beta-2 microglobulin, reflect a high tumor burden. Genetic constitution is the primary determinant of biologic behavior and, therefore, influences prognosis by a different mechanism than do measures of disease burden. Many staging systems, including the international staging system [87], use beta-2 microglobulin, but do not incorporate genetics.

Chromosome 13 deletion [del(13)] identified patients whose disease relapsed quickly following autotransplantation, including those who achieved remission [25]. Although the limited numbers and low proliferative rates of malignant plasma cells in marrow permit identification, by banding techniques, of abnormalities in less than 1/3 of patients, flouorescence in situ hybridization (FISH) identifies genomic abnormalities in approximately 90%. In combination with low beta-2 microglobulin, FISH identifies a group of patients lacking t(4;14) and del (17p), who have prolonged survival following tandem autotransplantation [88]. In contrast, patients with either genetic abnormality and a high beta-2 microglobulin fare poorly with this approach. In the largest series of myeloma patients analyzed for genomic abnormalities, the IFM was unable to demonstrate independent prognostic power of del(13). Its prognostic significance was related to its frequent association with abnormalities such as t(4;14) and del(17p) [88]. Further, this large study did not find an influence of t(11;14) on survival, in contrast to earlier less comprehensive studies [89,90].

Because allogeneic transplantation has been proven to be advantageous in high-risk patients with other hematologic malignancies, the IFM group prospectively compared autologous followed by dose-reduced allogeneic transplantation to tandem autologous transplantation in individuals with elevated B-2 microglobulin plus chromosome 13 abnormalities [66]. No advantage for allografting was detected. In Bruno's comparison in which treatments were assigned only according to the presence or absence of an HLA-identical sibling donor, neither chromosome 13 abnormalities nor B2-microglobulin levels influenced outcome after allografting [65], which yielded significantly better survival than tandem autografts. The suppression of graft-versus-myeloma by antithymocyte globulin, which was included in the preparative regimen of the former study, might contribute to these different results. Response to Bortezomib does not seem to correlate with specific unfavorable genetic abnormalities [91,92]. These data emphasize the need for further study of genetic alterations, their careful incorporation into risk assessment, and well-conceived study of their impact on specific therapeutic strategies.

CONCLUSION

Although this review summarizes available data on HSCT in multiple myeloma, it also identifies areas where critical information is unavailable. Data strongly support a benefit in PFS and TWiSTT for early autologous transplantation compared to conventional chemotherapy. Tandem transplantation appears to chiefly benefit patients with a limited response to first autotransplant. Allogeneic transplantation has become safer, and should be considered more frequently, particularly for younger patients early in the course of disease.

The influence of more effective induction regimens on the benefits of HSCT is uncertain. The question of whether patients who enter CR with modern induction therapy benefit from early autotransplantation is unanswered. Current prognostic staging

systems do not adequately incorporate known genomic aberrations and the basic mechanism and clinical relevance of many genetic alterations are uncertain. It is reasonable at present to use autotransplantation in those patients lacking high-risk genetic abnormalities where survival is prolonged following autotransplantation, and to perform tandem transplants in those who fail to achieve at least a very good PR. Bortezomib-based combination regimens should be used early in patients with adverse prognostic features, including genetics. All of these issues require prospective study and emphasize the need for sound, large prospective multinstitutional trials. Substantial additional work is needed to develop better prognostic classification systems to rationally study risk-adapted therapies.

The aim of these trials is not to develop simplistic treatment algorithms. Individually tailored treatment is the goal: no single feature, its quantation, or some arithmetic sum of measured features should finalize decisions on treatment. The constellation of individual features that distinguish a patient must be considered in light of clinical experience and judgment. Basic work can and will provide information needed to make better decisions.

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